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Haemodynamic effects of the antiarrhythmic quaternary ammonium compound QX-572 in man

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The haemodynamic effects of N,N-bis(phenyl-carbamoylmethyl) dimethylammonium chloride (QX-572) in man were studied. A controlled study was performed to rule out a possible influence of the catheterization procedure as such on the results. Ten patients with mild to moderate aortic regurgitation were studied: based on clinical data the patients were divided into 2 groups of 5. Randomly it was decided that one group should constitute a control group receiving saline while the second group received QX-572 8 mg/kg body weight. In both groups the administration was performed as a slow intravenous infusion during 30 minutes. Heart rate, pressures in brachial artery and right atrium, cardiac output, stroke volume, and systemic vascular resistance were determined before, during, and up to 30 minutes after completion of placebo or QX-572. These variables remained stable in the control group while QX-572 produced an increase in heart rate most pronounced at the end of the infusion period, a transient decrease in systolic and mean brachial artery pressure during the infusion, and during the same period a decrease in right atrial pressure. Cardiac output and systemic vascular resistance were unchanged by QX-572 but they were not measured during the infusion when the changes in pressures were most pronounced. QX-572 was thought to act as a peripheral vasodilator during the infusion. Left ventricular contractility was studied by means of pressure curves obtained from a catheter tip manometer placed in the left ventricle. The first derivative of the isovolumic left ventricular pressure at the highest level (45 mmHg) common to all patients was used (dp/dt-45). No significant difference could be observed when comparing mean changes of dp/dt-45 for the two groups. In the control group there was a slight but significant increase in dp/dt-45 during the time of observation. In the QX-572 group the results varied between individuals. Two of the patients differed from all other patients in the control and the QX-572 groups showing a decrease in dp/dt-45 which, when most pronounced at the end of the infusion period, was −31 and −28 per cent of the preinfusion levels, respectively. This decrease probably reflects reduction of contractility. It was concluded that QX-572 in a dose of 8 mg/kg body weight did not have any major haemodynamic drawbacks.

The lignocaine derivative, N,N-bis (phenylcarbamoylmethyl) dimethylammoniumchloride (QX-572)[2] has been shown to be active against ventricular tachyarrhythmias (Katz, 1965; Schwartz, Stapleton, and Covino, 1967). In a recent study the drug was remarkably effective in the treatment of serious, refractory ventricular tachyarrhythmias, and its duration of action was long (Rydén *et al.*, 1974a). A limitation of commonly used antiarrhythmic drugs is reduction of cardiac contractility or other unfavourable haemodynamic effects. This sometimes precludes the use of sufficiently high doses to suppress arrhythmia (Mason *et al.*, 1973). QX-572 has been claimed to possess a positive inotropic effect (Katz, 1963). However, it has also been found that a rapid rate of injection can produce peripheral vasodilatation and a concomitant drop in blood pressure (Schwartz *et al.*, 1967). These findings are to a large extent based on studies on dogs. No detailed haemodynamic investigations have so far been performed in man. Directional changes in cardiac performance caused by the administration of antiarrhythmic drugs are often evaluated by means of their influence on pressures and cardiac output. Peripheral effects have, however, a great influence on cardiac output,

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[2] Manufactured by Astra.

and compensatory mechanisms may mask the influence of the intervention (Sonnenblick, Parmley, and Urschel, 1969). When planning the investigation of the haemodynamic effects of QX-572, it was felt that a more complete picture could be gained by adding to the measurement of flow and pressures an analysis of the contractile state of the myocardium.

In the present study the pressures in the brachial artery, right atrium, and left ventricle as well as heart rate, cardiac output, and systemic vascular resistance have been studied in man. Left ventricular contractility indices have been derived from pressure curves obtained by means of a catheter tip manometer placed in the left ventricle. To rule out the possible influence of the procedure as such on the results the study has been performed in a controlled manner.

Subjects and methods

Observations were made on 10 patients with aortic insufficiency after informed consent had been obtained. Selected data from the patients are presented in Table 1. On clinical grounds the degree of aortic regurgitation was considered mild in Cases 2, 3, 6, and 9. In the remaining cases it was judged as moderate. The study of QX-572 was performed as part of a routine cardiac catheterization. This was either a postoperative evaluation of valvular surgery with fascia lata prosthesis (Cases 1, 2, 3, 4, 6, 7, and 9) or a clinical evaluation of aortic insufficiency (Cases 5, 8, and 10). None of the patients had aortic stenosis or mitral valvular disease.

Before catheterization the patients were divided into two comparable groups. This division was based upon clinical history with functional classification according to the New York Heart Association (1964), physical examination performed independently on the same day by two examiners, *x*-ray of the chest, and electrocardiogram. Randomly, it was decided that one group of patients (Cases 1–5, Table 1) should constitute a control group while the patients in the other group (Cases 6–10, Table 1) were given QX-572. All catheterizations were performed in the nonsedated, postabsorptive state, with the patients in the supine position. All drugs were withheld for at least 12 hours before the study. A polyethylene catheter (PE 205) was introduced percutaneously into a brachial artery. A flow directed 5 F Swan-Ganz catheter (Edwards Laboratories, Santa Ana, U.S.A.) was used for pressure recordings in the right atrium and dye injections. Right atrial pacing at double the threshold of stimulation was performed via a bipolar pacemaker electrode (USCI, C 51, 5 F) positioned close to the sinus node. A Statham SF–1 catheter tip manometer was placed in the left ventricle by transseptal catheterization via the right subclavian vein (Kvasnička *et al.*, 1973). This manometer had a resonance frequency of approximately 5 kHz. The fluid-filled arm of the SF–1 catheter, the brachial artery catheter, and the Swan-Ganz

TABLE 1 *Selected data from patients*

Case No.	*Age (yr), sex*	*Diagnosis*	*Funct. class**	*Blood pressure (mmHg)*	S_3	*Presystolic murmur or* S_4	*Chest x-ray*	
							Heart volume (ml/ml per BSA)	*Pulmonary congestion*
1	30 M	Aortic regurgitation; fascia lata	I	125/65	+++	−	1230/730	++
2	52 M	Aortic regurgitation; fascia lata	II	120/65	−	−	1260/690	−
3	32 M	Aortic regurgitation; fascia lata	I	160/60	+	+	1060/550	−
4	53 F	Aortic regurgitation; fascia lata	III	145/80	−	−	1150/690	−
5	49 M	Aortic regurgitation	II	160/60	−	++	1030/520	−
6	42 M	Aortic regurgitation; fascia lata	II	180/70	−	+++	840/420	−
7	49 M	Aortic regurgitation; fascia lata	I	140/75	−	−	1240/570	−
8	52 M	Aortic regurgitation	III	145/70	−	+	1180/715	−
9	60 M	Aortic regurgitation; fascia lata	I	160/75	−	−	1750/800	−
10	50 F	Aortic regurgitation	III	170/80	−	+	830/500	−

* According to the New York Heart Association.
− = not present; + = mild; ++ = moderate; +++ = pronounced; S_3 = third heart sound; S_4 = fourth heart sound; BSA = body surface area (m^2); LVH = left ventricular hypertrophy; AVI = atrioventricular block of first degree; RBBB = right bundle-branch block.

catheter were attached to Statham P-23dB transducers connected to Beckman type 9855 amplifiers with preamplifiers of type Beckman 481 B. All pressures and the electrocardiogram were recorded on an Ultralette recorder, type ABEM-1610 and stored on a Honeywell 5600 FM tape recorder. The data from the manometer were played back from the tape to a Digital Equipment Corporation PDP 15 for further processing as previously described in detail (Broman *et al.*, 1974). In short, a power spectrum was obtained for each individual beat, and an optional cut-off frequency with regard to this and the level of noise was used. The computer then calculated and digitally and graphically presented various isovolumic contractility indices. Of these the first derivative of the isovolumic left ventricular pressure (dp/dt; mmHg/sec) at the highest level common to all patients was used. The left ventricular enddiastolic pressure was measured just before the rapid pressure rise during ventricular contraction, i.e. at the top of or after the a wave. The highest point of the systolic pressure wave was taken as the left ventricular systolic pressure. The mean pressures in the brachial artery and right atrium were obtained by electrical integration. The reference zero level was set at 5 cm below the angle of Louis. The cardiac output was determined by the dye dilution method using indocyanine green as the indicator. The calculations were performed by the standard method for dilution curves after correction for haematocrit (Forsberg, 1964). Systemic vascular resistance was calculated as the difference between the mean brachial artery and the mean right atrial pressures divided by the cardiac output and was expressed in units. After the final positioning of the catheters the patients rested for 20 minutes to achieve a steady state. The brachial artery and right atrial pressures, heart rate, cardiac output, stroke volume, and systemic vascular resistance were then determined during spontaneous heart rate. After atrial pacing for 30 seconds at a rate between 100 and 120 beats/minute, a 10-second recording was obtained of the brachial artery and the left ventricular pressures to obtain the curves for contractility calculations. The patients then received QX-572 or saline by infusion over 30 minutes. The infusion rate was kept constant by means of an infusion pump (Infusomat, Braun, Melsungen, West Germany). QX-572 was administered in a total dose of 8 mg/kg body weight as a 5 per cent solution in saline in an arm vein via a previously introduced short polyethylene cannula. The recordings of heart rate, blood pressures, and left ventricular curves were obtained at 15, 30, 45, and 60 minutes after the start of drug administration, while cardiac output, stroke volume, and systemic vascular resistance were determined at 30, 45, and 60 minutes.

Statistical comparisons within the respective groups of patients were made according to Student's t-test for paired differences. For comparisons between the groups t-test for independent means was used.

Electro cardio-gram	*Drugs*	*Drugs during study*
LVH	Digoxin 0·25 mg/day	NaCl 0·9% 104 ml
LVH	Digoxin 0·125 mg/day; procainamide 2·0 g/day	NaCl 0·9% 112 ml
LVH	Digoxin 0·25 mg/day	NaCl 0·9% 120 ml
LVH	Digoxin 0·25 mg/day	NaCl 0·9% 112 ml
Normal	Digitoxin 0·1 mg/day	NaCl 0·9% 128 ml
Normal	Digitoxin 0·1 mg/day	QX-572 640 mg
LVH	Digoxin 0·25 mg/day; procainamide 2·0 g/day	QX-572 648 mg
LVH AVI	Digitoxin 0·1 mg/day; quinidine 1·2 g/day	QX-572 536 mg
LVH	Digoxin 0·25 mg/day	QX-572 768 mg
RBBB	Digoxin 0·25 mg/day	QX-572 496 mg

Results

Heart rate, pressures in brachial artery and right atrium, cardiac output, stroke volume, and systemic vascular resistance are presented in Table 2 for the control group and in Table 3 for the QX-572 group. Table 4 contains left ventricular pressures, the aortic valve opening pressure, and dp/dt for the control group. The corresponding data from the QX-572 group can be found in Table 5. The opening of the aortic valve (Table 4 and 5) never occurred at or below 45 mmHg. Therefore, the dp/dt was studied at that level (dp/dt-45). On those occasions when the maximal dp/dt occurred before the opening of the aortic valve there was a good correlation between this variable and dp/dt-45 ($r = 0{\cdot}95$; dp/dt-45 = 0·72 . dp/dt max + 274; $P < 0{\cdot}001$). The left ventricular curves were computerized from the lowest possible paced rate. In the control group (Table 4) all data were obtained from a rate of 100/min except in Case 5 (110/min). In the QX-572 group (Table 5) in which heart rate was increased by the drug the paced rate was 115/min except in Case 9 (120/min) and Case 10 (100/min). Some interference was observed between pacemaker and spontaneous rhythm at 30 minutes for Case 6, and at 15 and 30 minutes for Case 9. In Case 6 (Table 5) the catheter tip manometer was withdrawn from the left side of the heart 38 minutes after the start of infusion since there were suspicions of clots within the catheter.

TABLE 2 *Heart rate, brachial artery, and right atrial pressures, cardiac output, stroke volume, and systemic vascular resistance in control group*

		1	2	3	4	5	Mean	SD	SE	Difference† P<
Heart rate (beats/min)	C	81	64	96	77	76	79	11·5	5·1	
	15	86	66	96	76	84	82	11·3	5·1	NS
	30	82	66	90	78	77	79	8·7	3·9	NS
	45	78	64	90	76	76	77	9·2	4·1	NS
	60	78	66	90	80	80	78	8·5	3·8	NS
Right atrial pressure (mmHg)	C	6	2	1	5	1	3	2·3	1·0	
	15	6	2	2	6	1	3	2·4	1·1	NS
	30	5	1	1	5	1	3	2·2	1·0	NS
	45	5	2	2	7	1	3	2·5	1·1	NS
	60	6	1	1	5	0	3	2·7	1·2	NS
Brachial artery pressure (mmHg) Systolic	C	109	134	138	142	120	129	13·7	6·1	
	15	106	134	132	165	130	133	21·0	9·4	NS
	30	105	143	131	159	123	132	20·4	9·1	NS
	45	106	132	140	153	126	131	17·4	7·8	NS
	60	110	139	128	140	131	130	12·1	5·4	NS
Diastolic	C	51	45	72	63	44	55	12·1	5·4	
	15	53	48	65	59	54	56	6·5	2·9	NS
	30	48	52	66	58	46	54	8·1	3·6	NS
	45	44	41	71	62	47	53	12·9	5·8	NS
	60	52	42	60	46	61	52	8·4	3·7	NS
Mean	C	72	77	95	86	77	81	9·1	4·1	
	15	77	70	86	90	86	82	8·1	3·6	NS
	30	72	76	82	97	83	82	9·5	4·3	NS
	45	75	73	93	95	78	83	10·4	4·7	NS
	60	74	76	86	85	84	81	5·6	2·5	NS
Cardiac output (l/min)	C	3·9	3·3	9·7	3·3	7·5	5·5	2·9	1·3	
	30	4·2	3·7	9·2	3·7	6·7	5·5	2·4	1·1	NS
	45	3·5	4·0	8·7	3·8	7·3	5·5	2·4	1·1	NS
	60	3·8	—*	9·1	3·4	8·1	6·1	2·9	1·5	NS
Stroke volume (ml)	C	48	52	101	43	99	69	28·8	12·9	
	30	51	56	102	47	87	69	24·4	10·9	NS
	45	45	63	97	50	96	70	24·9	12·9	NS
	60	49	—*	101	43	101	74	31·8	14·2	NS
Systemic vascular resistance units	C	17	23	10	25	10	17	7·0	3·1	
	30	16	20	9	25	12	16	6·3	2·8	NS
	45	20	18	11	23	11	17	5·4	2·4	NS
	60	18	—*	9	24	10	15	7·1	3·1	NS

* Technical failure.
† Compared to the control level.
C = control observation.

Comparing the two groups, the control levels of the haemodynamic and contractility variables (Table 2 and 3; Table 4 and 5) did not differ significantly, with one exception. In the control group the dp/dt-45 was 1234 ± 153 mmHg/sec (mean ± SE) and the corresponding level for the QX-572 group was 1764 ± 146 mmHg/sec ($P < 0.05$).

The mean differences ± SE for the two groups between the control observations and the results obtained during and after the infusion of saline and QX-572 are presented in Fig. 1 to 3. In the control group there was a slight but significant increase of dp/dt-45 at 30 ($P < 0.05$) and at 60 ($P < 0.05$) minutes after the start of infusion (Table 4). The maximal individual changes of dp/dt-45 were for the control Cases 1 to 5 as a percentage of the control value, +50, +14, +20, +2, and +20, respectively (Table 4). In the control group all other variables remained stable.

In the QX-572 group there was an increase of heart rate which was most pronounced at the end of the infusion period. This increase in heart rate diminished but was still significant at the end of the observation period (Fig. 1). Cardiac output and systemic vascular resistance did not change significantly while stroke volume was reduced after the drug. QX-572 caused a transient decrease in systolic and mean brachial artery pressure during the infusion which, however, was significant only at 15 minutes. Right atrial pressure decreased signi-

TABLE 3 *Heart rate, brachial artery, and right atrial pressures, cardiac output, stroke volume, and systemic vascular resistance in QX-572 group*

Case No.		*6*	*7*	*8*	*9*	*10*	*Mean*	*SD*	*SE*	*Difference* P<*
Heart rate (beats/min)	C	64	72	85	75	70	73	7·7	3·5	
	15	102	110	108	122	70	102	19·5	8·7	0·05
	30	120	108	104	122	72	105	20·1	9·0	0·05
	45	82	92	92	94	76	87	7·8	3·5	0·01
	60	76	86	86	92	72	82	8·2	3·7	0·05
Right atrial pressure (mmHg)	C	2	1	−1	−2	4	1	2·4	1·1	
	15	0	−1	−2	−4	1	−1	1·9	0·9	0·001
	30	0	−2	−3	−2	2	−1	2·0	0·9	0·05
	45	2	0	−1	−3	4	0	2·7	1·2	NS
	60	2	−2	0	−2	4	0	2·6	1·2	NS
Brachial artery pressure (mmHg) Systolic	C	131	133	142	180	141	145	19·9	8·9	
	15	133	109	108	161	100	122	25·0	11·2	0·05
	30	144	143	89	174	96	129	35·8	15·0	NS
	45	154	140	126	194	133	149	27·0	12·1	NS
	60	158	133	138	184	147	152	20·3	9·1	NS
Diastolic	C	61	66	55	67	57	61	5·3	2·4	
	15	65	40	55	77	49	57	14·3	6·4	NS
	30	69	78	48	86	50	66	16·8	7·5	NS
	45	71	85	55	86	67	73	13·0	5·8	0·01
	60	67	77	55	82	71	70	10·3	4·6	NS
Mean	C	92	87	92	108	90	94	8·2	3·7	
	15	90	66	75	97	67	79	13·9	6·2	0·05
	30	96	97	57	106	68	85	21·1	9·4	NS
	45	104	102	80	118	84	98	15·5	7·0	NS
	60	107	84	88	122	90	98	15·9	7·1	NS
Cardiac output (l/min)	C	5·3	5·9	4·9	7·5	5·4	5·8	1·0	0·5	
	30	7·2	7·2	4·8	8·6	4·9	6·5	1·6	0·7	NS
	45	6·5	6·7	5·0	8·6	5·3	6·4	1·4	0·6	NS
	60	5·9	6·4	4·9	7·8	5·0	6·0	1·2	0·5	NS
Stroke volume (ml)	C	83	82	58	100	77	80	15·0	6·7	
	30	60	67	46	70	68	62	9·8	4·4	0·01
	45	79	73	54	91	70	73	13·5	6·0	0·05
	60	78	74	57	85	69	73	10·5	4·7	0·05
Systemic vascular resistance units	C	17	15	19	15	16	16	1·7	0·7	
	30	13	14	13	13	14	13	0·5	0·2	NS
	45	16	15	16	14	15	15	0·8	0·4	NS
	60	18	13	18	16	17	16	2·1	0·9	NS

* Compared to the control level.
C = control observation.

ficantly during the administration of QX-572 but returned to control levels within 15 minutes after the end of infusion. The left ventricular systolic and end-diastolic pressure and the opening pressure of the aortic valve did not change significantly from the control level in the QX-572 group (Fig. 3). dp/dt-45 also remained stable. Despite the changes observed in the saline group as regards dp/dt-45, no significant difference between the two groups could be noted. The maximal changes in dp/dt-45 for the QX-572 Cases 6 to 10 were, as a percentage of the control value, +37, +13, −31, +7, and −28, respectively.

Side effects

All patients who received QX-572 except Case 9 experienced slight circumoral paraesthesia and numbness of the tongue from 15 to 20 minutes after the start of infusion and lasting about 10 to 15 minutes after the completion of drug infusion. One patient (Case 6) complained of dizziness for 10 minutes from 25 minutes after the start of infusion. In the control group no side effects were observed.

Discussion

There are very few studies available concerning the haemodynamic properties of QX-572. Katz (1963)

TABLE 4 *Left ventricular pressures, aortic valve opening pressure, and dp/dt-45 obtained in control group during atrial pacing*

Case No.		*1*	*2*	*3*	*4*	*5*	*Mean*	*SD*	*SE*	*Difference* P<*
Paced rate beats/min		100	100	100	100	110				
Left ventricular pressure (mmHg) Systolic	C	123	128	125	143	134	131	8·1	3·6	
	15	116	133	121	175	138	137	23·2	10·4	NS
	30	117	145	130	156	136	137	14·8	6·6	NS
	45	113	139	120	149	134	131	14·5	6·5	NS
	60	116	138	112	153	136	131	16·9	7·6	NS
End-diastolic	C	33	6	12	18	12	16	10·3	4·6	
	15	31	4	11	24	10	16	11·1	5·0	NS
	30	31	8	14	22	10	17	9·5	4·2	NS
	45	24	8	11	20	7	14	7·6	3·4	NS
	60	27	6	12	19	10	15	8·3	3·7	NS
Aortic valve opening pressure (mmHg)	C	51	62	72	68	55	62	8·7	3·9	
	15	50	56	68	70	97	68	18·1	8·1	NS
	30	50	60	72	65	58	61	8·2	3·7	NS
	45	50	63	70	65	57	61	7·7	3·4	NS
	60	52	65	65	67	57	61	6·4	2·9	NS
dp/dt-45 (mmHg/sec)	C	780	1133	1442	1132	1681	1234	342	153	
	15	736	1200	1436	1188	1818	1276	395	177	NS
	30	1025	1297	1468	1202	1772	1353	284	127	0·05
	45	1167	1213	1440	1361	1849	1406	271	121	NS
	60	1030	1228	1436	1268	1952	1383	349	156	0·05

C = control observation.
* Compared to the control level.

TABLE 5 *Left ventricular pressures, aortic valve opening pressure, and dp/dt-45 obtained in the QX-572 group during atrial pacing*

Case No.		*6**	*7*	*8*	*9*	*10*	*Mean*	*SD*	*SE*	*Difference† P<*
Paced rate beats/min		115	115	115	120	100				
Left ventricular pressure (mmHg) Systolic	C	130	142	166	150	125	143	16·4	7·3	
	15	134	151	136	162	90	135	27·4	12·3	NS
	30	155	152	113	154	84	132	31·9	14·3	NS
	45	—	149	144	177	127	150	25·4	12·7	NS
	60	—	140	154	182	118	149	26·8	13·4	NS
End-diastolic	C	5	10	9	10	6	8	2·3	1·0	
	15	1	8	5	14	6	7	4·8	2·1	NS
	30	6	8	7	8	5	7	1·3	0·6	NS
	45	—	10	5	12	7	9	3·1	1·6	NS
	60	—	3	4	12	12	8	4·9	2·5	NS
Aortic valve opening pressure (mmHg)	C	77	52	67	74	68	68	9·7	4·3	
	15	70	56	51	83	55	63	13·3	5·9	NS
	30	78	56	49	83	50	63	16·1	7·2	NS
	45	—	56	57	101	69	71	21·0	10·5	NS
	60	—	77	55	101	67	75	19·5	9·8	NS
dp/dt-45 (mmHg/sec)	C	2315	1784	1517	1665	1540	1764	326	146	
	15	2637	2024	1443	1650	1213	1800	572	256	NS
	30	3166	2019	1048	1747	1116	1819	859	384	NS
	45	—	1991	1390	1779	1363	1630	306	137	NS
	60	—	1804	1548	1757	1350	1614	208	104	NS

C = control observation.
* SF1 catheter withdrawn at 38 minutes; see text.
† Compared to the control level.

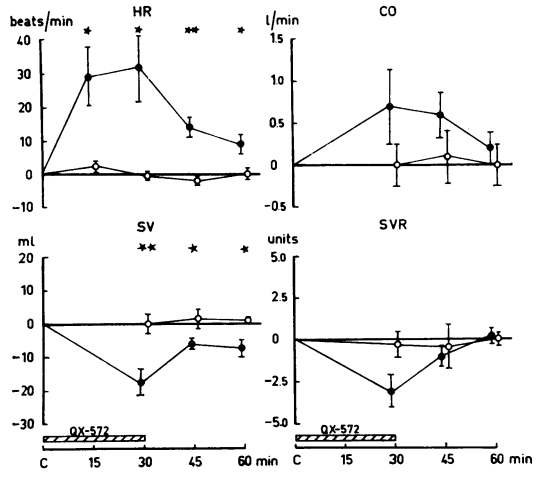

FIG. 1 *Mean difference ± SE between the control and postinfusion observations of heart rate (HR), cardiac output (CO), stroke volume (SV), and systemic vascular resistance (SVR). ○ = control group; ● = QX-572 group; * = P < 0·05; ** = P < 0·01; *** = P < 0·001. The notations about the degree of significance refer to the comparison of the mean differences obtained in the saline and QX-572 groups.*

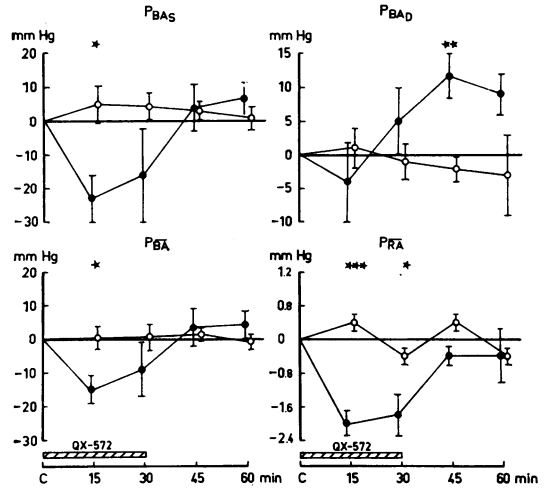

FIG. 2 *Mean differences ± SE between the control and postinfusion observations of systolic (P_{BA_S}), diastolic (P_{BA_D}), and mean ($P_{\overline{BA}}$) pressure in brachial artery and right atrial mean pressure ($P_{\overline{RA}}$). Symbols as in Fig. 1.*

reported an increase in myocardial contractility and coronary sinus blood flow, while heart rate, arterial blood pressure, and cardiac output were unchanged after intracoronary injection of 0·2 mg/kg of QX-572 in dogs. Contractility was measured with a strain gauge sutured on to the myocardium (R. L. Katz, 1974, personal communication). In another study performed by Schwartz *et al.* (1967) intravenous administration of QX-572, 2 to 8 mg/kg, in dogs caused a transient drop in arterial pressure related to a drop in systemic vascular resistance. Cardiac output remained unchanged by the drug. They concluded that QX-572 was devoid of cardiac depressant effects but had a direct vasodilator action. The hypotensive effect was related to the rate of infusion. That QX-572 acts as a vasodilator is supported by the present findings during the infusion period. This effect can explain the fall in right atrial as well as systolic and mean brachial artery pressures. The lack of a significant decrease in systemic vascular resistance does not preclude this statement since, according to the protocol, cardiac output and vascular resistance were not measured at the point of maximal hypotension. One of the most constant and striking effects of a QX-572 infusion is the increase in heart rate (Katz, 1965; Schwartz *et al.*, 1967; Rydén *et al.*, 1974a) which was also obvious in the present study. Another effect also observed earlier (Schwartz *et al.*, 1967; Rydén *et al.*, 1974a) is the increase in diastolic pressure of the brachial artery observed after the completion of infusion. On the other hand the earlier suggestion that QX-572

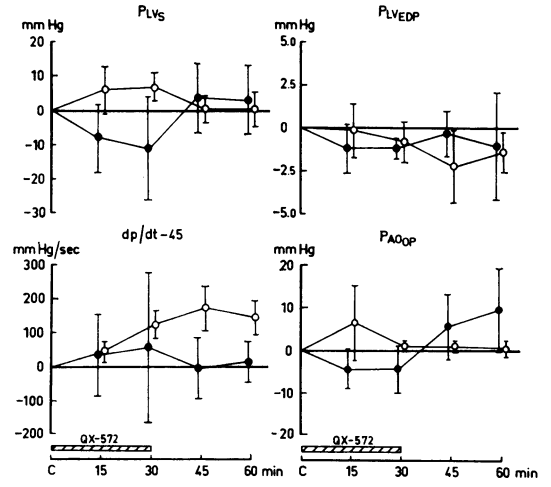

FIG. 3 *Mean differences ± SE between the control and postinfusion observations of the systolic (P_{LV_S}) and the end-diastolic ($P_{LV_{EDP}}$) pressure in the left ventricle, aortic valve opening pressure ($P_{AO_{OP}}$), and dp/dt-45. Symbols as in Fig. 1.*

has a positive inotropic action was not confirmed by the present study.

When discussing the lack of agreement in results, methodological aspects must be considered first of all. The procedure of the present study included a catheterization for 3 to 4 hours. It is always difficult to know whether any observed changes are caused by the intervention (in this case the administration of QX-572) or merely reflect unstable conditions induced by tiredness and discomfort from the investigation as such. However, the control group remained stable in all respects except that dp/dt-45 increased slightly, perhaps because of an increase of sympathetic tone.

The fact that changes in the rate of pressure rise (dp/dt) during the isovolumic part of the ventricular contraction reflect changes in contractility has been extensively discussed (Reeves *et al.*, 1960; Mason, 1969; Furnival, Linden, and Snow, 1970; Krayenbuehl *et al.*, 1973). Since the more commonly used dp/dt max in some cases was not reached before the opening of the aortic valve, the dp/dt at the highest calculated pressure common for all patients before and after the intervention was used. Before any conclusions can be drawn from the data obtained certain requirements must be met. The pressure curves must be obtained with a catheter tip manometer to avoid distortions and to ensure a sufficiently high frequency response (Gleason and Braunwald, 1962). The system used in the present study with individual cut-off frequencies and digital treatment of the data fulfils these demands (Broman *et al.*, 1974). Pre- and afterload should be constant. With the left ventricular end-diastolic pressure and the opening pressure of the aortic valve essentially stable, it is likely that this requirement was fulfilled during the period of observation. Since contractility is also influenced by heart rate (Furnival *et al.*, 1970), this was kept constant while recording the left ventricular curves. One explanation for the somewhat higher control dp/dt-45 levels in the QX-572 group may be the faster rate of pacing in that group compared to the control group. It seems unlikely that the disparity in paced rate would mask a difference in change of contractility caused by saline and QX-572 (Edman, 1965). In severe aortic regurgitation the value of contractility indices derived from pressure recordings has been questioned (Mason, Spann, and Zelis, 1970a), while moderate insufficiency is thought not to invalidate contractility measurements (Krayenbuehl *et al.*, 1973). With these considerations in mind, it seems unlikely that shortcomings of the method would explain the disparity between previous and present results as regards the effect of QX-572 on myocardial contractility.

Most antiarrhythmic drugs behave as depressants on myocardial performance and these effects are dose dependent (Hammermeister, Boerth, and Warbasse, 1972; Mason *et al.*, 1970b). Thus, the lack of agreement may only reflect differences in doses. The intracoronary injection of QX-572 (0·2 mg/kg) used by Katz (1963) was calculated to correspond to coronary concentrations after administration of 2 mg/kg intravenously. In the present study QX-572 was given in a dose of 8 mg/kg. In the study performed by Schwartz *et al.* (1967) the dose was up to 8 mg/kg but the conclusions were based exclusively on flow and pressure data. Furthermore, these two studies were performed on dogs, and species differences may exist.

In the present investigation QX-572 in a dose of 8 mg/kg body weight did not reveal any depressant effects on cardiac contractility as judged from the comparison of mean levels in the groups. Turning to individual patients it was found, however, that the effect on dp/dt-45 varied. Two cases (8 and 10) showed a decrease in dp/dt-45 which was most pronounced at the end of the infusion period. This decrease might reflect a reduction in contractility. In this respect they differed from the other patients in the QX-572 group as well as from the control group. The response to QX-572 in the two patients showing a decrease in dp/dt-45 differed also in other respects. The heart rate in Case 10 did not increase and for both Cases 8 and 10 the decrease in the pressure of the brachial artery was more pronounced than for the other patients in the QX-572 group. It should be kept in mind that the observed effects of QX-572 are net effects. Different mechanisms of actions of the drug may interact. It has recently been shown that QX-572 causes a decrease in the effective refractory periods in the atrium, atrioventricular node, and ventricle (Rydén, Olsson, and Kvasnička, 1974b). A possible explanation for these findings is that QX-572 in some way increases sympathetic drive. This hypothesis does have experimental support since it is possible to abolish the increase in heart rate induced by QX-572 in cats by pretreatment with propranolol (U. Eliasson and L. Rydén, unpublished data). If there is a dual working mechanism a direct negative inotropic effect of QX-572 might be masked by the increased sympathetic drive which will increase contractility. If this is true the explanation for the varying individual responses to QX-572 might be dominance of either increased sympathetic drive or a direct effect of the drug.

In conclusion, QX-572 in a dose (8 mg/kg) effective against ventricular arrhythmias (Rydén *et al.*, 1974a) did not reveal any major haemodynamic drawbacks in man. The observed increase in heart rate was short lasting. During the infusion a transient

decrease in brachial artery pressure was observed. The haemodynamic response to QX-572 differed in some respects between individual patients and an explanation for this may be a dual mechanism for the action of the drug.

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References

Broman, H., Kvasnička, J., Liander, B., and Varnauskas, E. (1974). A computerized system for optimal filtering of left ventricular pressure data. *Research Laboratory of Medical Electronics, Göteborg, Technical report* 2: 74.

Edman, K. A. P. (1965). Drugs and properties of heart muscle. *Annual Review of Pharmacology*, **5**, 99.

Forsberg, S-Å. (1964). Pulmonary blood volume in man. *Acta Medica Scandinavica*, **175**, Suppl. 410.

Furnival, C. M., Linden, R. J., and Snow, H. M. (1970). Inotropic changes in the left ventricle: the effect of changes in heart rate, aortic pressure and end-diastolic pressure. *Journal of Physiology*, **211**, 359.

Gleason, W. L., and Braunwald, E. (1962). Studies on the first derivative of the ventricular pressure pulse in man. *Journal of Clinical Investigation*, **41**, 80.

Hammermeister, K. E., Boerth, R. C., and Warbasse, J. R. (1972). The comparative inotropic effects of six clinically used antiarrhythmic agents. *American Heart Journal*, **84**, 643.

Katz, R. L. (1963). Cardiovascular action of N,N-bis (phenylcarbamoylmethyl) dimethyl ammonium chloride (QX-572). *Pharmacologist*, **5**, 260.

Katz, R. L. (1965). Antiarrhythmic and neuromuscular effects of QX-572 in man. *Acta Anaesthesiologica Scandinavica*, **9**, 73.

Krayenbuehl, H. P., Rutishauser, W., Wirz, P., Amende, I., and Mehmel, H. (1973). High-fidelity left ventricular pressure measurements for the assessment of cardiac contractility in man. *American Journal of Cardiology*, **31**, 415.

Kvasnička, J., Liander, B., Rydén, L., and Varnauskas, E. (1973). A technique for transseptal left heart catheterization with a catheter tip manometer. *Cardiovascular Research*, **7**, 723.

Mason, D. T. (1969). Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. *American Journal of Cardiology*, **23**, 516.

Mason, D. T., DeMaria, A. N., Amsterdam, E. A., Zelis, R., and Massumi, R. A. (1973). Antiarrhythmic agents. II: Therapeutic considerations. *Drugs*, **5**, 292.

Mason, D. T., Spann, J. F., and Zelis, R. (1970a). Quantification of the contractile state of the intact human heart. Maximal velocity of contractile element shortening determined by the instantaneous relation between the rate of pressure rise and pressure in the left ventricle during isovolumic systole. *American Journal of Cardiology*, **26**, 248.

Mason, D. T., Spann, J. F., Zelis, R., and Amsterdam, E. A. (1970b). Effects of antiarrhythmic drugs on myocardial performance in man: assessment by the maximal velocity of contractile element shortening (abstract). *American Journal of Cardiology*, **25**, 114.

New York Heart Association, Criteria Committee (1964). *Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for Diagnosis*, 6th ed. Little, Brown, Boston.

Reeves, T. J., Hefner, L. L., Jones, W. B., Coghlan, C., Prieto, G., and Carroll, J. (1960). The haemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction. *American Heart Journal*, **60**, 745.

Rydén, L., Hjalmarson, Å., Wasir, H., and Werkö, L. (1974a). Effects of a long-acting antiarrhythmic agent – QX-572 – on therapy resistant ventricular tachyarrhythmias. *British Heart Journal*, **36**, 811.

Rydén, L., Olsson, B., and Kvasnička, J. (1974b). Electrophysiological effects of the antiarrhythmic agent QX-572 in the heart in man with special reference to rate induced changes in effective refractory periods. *Cardiovascular Research*. In the press.

Schwartz, M. L., Stapleton, J., and Covino, B. G. (1967). Clinical pharmacology of N,N-bis (phenylcarbamoylmethyl) dimethyl ammonium chloride (QX-572). A new antiarrhythmic agent. *Journal of Clinical Pharmacology*, **7**, 278.

Sonnenblick, E. H., Parmley, W. W., and Urschel, C. W. (1969). The contractile state of the heart as expressed by force-velocity relations. *American Journal of Cardiology*, **23**, 488.

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